Amendments to the drawings:

Replacement drawing sheets containing Figs. 1B, 2 and 6 are enclosed, to replace the corresponding drawing sheets currently on file.

REMARKS

The applicants have carefully studied the outstanding Office Action. The present amendment is intended to be fully responsive to all points of rejection raised by the Examiner, and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application are respectfully requested.

Drawing amendments

Fig. 1B has been amended by addition of the legend "Prior art" as requested by the Examiner.

In Fig. 2, the filter wheel labeled as 27 has been correctly relabeled as 12.

In Fig. 6, the legend "Prior art" has been deleted.

Claim amendments

Claims 34 and 35 have been amended by the addition of the recitation of the source from which the known refractive index variations are determined, namely any one of differential interference contrast (DIC) imaging, phase microscopy or fluorescence microscopy. Support for this amendment is to be found in the specification on page 5, paragraph 2.

Claim rejections - 35 USC § 112

The Examiner has stated that "Claims 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 38, which is representative of claim 39, will be exemplified.

Claim 38 requires:

an adaptive optics controller to control an adaptive optical element in a confocal microscope to correct aberrations resulting from variations in the refractive index at a multiplicity of locations in a medium; where

the adaptive optics controller uses an aberrated wavefront determined by the ray tracer.

The entirety of the specification is directed to correcting aberrations resulting from refractive index variations using image processing. For example, refer to figure 2, numeral 34, figure 3, numeral 54 and figure 7. That is, in order to correct the aberrations, a location dependent point spread function is convoluted with an observed image as depicted at figure 3, numeral 54. This is a mathematical manipulation and reconstruction.

However, claim 38 requires a physical, or optical element to be placed in the optical path of a confocal microscope which is adaptive and responsive to the aberrated wavefront (presumably as determined using image processing techniques) to perform the deconvolution step at figure 3, numeral 54. The optical element that performs this deconvolution is not sufficiently described by the specification to enable one skilled in the art to make and use the invention without undue experimentation."

The applicants respectfully submit that the assertion of the Examiner in the last quoted paragraph is incorrect on two counts. In the first place, the apparatus claimed in claim 38 differs from that claimed in the previous claims in that it is not based on a mathematical manipulation and reconstruction, as asserted by the Examiner. Claim 38 and its base claim 34 do not recite the image processing techniques as recited in the previous claims in order to correct the aberrations in the observed image, but rather only the analytical ray tracing without calculating the point spread function and without performing deconvolution. Secondly, instead of the mathematical reconstruction, claim 38 recites in a confocal microscope, the use of an adaptive optical element which is controlled by means of the aberrated wavefront derived from the ray tracing apparatus of claim 34, thereby to correct aberrations resulting from the variations in the refractive index. The applicants respectfully submit that many kinds of such adaptive optics elements are well known to one of skill in the art, such as are

described in the book by R.K. Tyson entitled "Principles of Adaptive Optics", Academic Press, New York, 1991, which is referenced in the Background section of the application. Such elements do not therefore need further elaboration in order to enable the claim. Examples of such adaptive optical elements include spatial light modulators, which generate a spatially variable phase shift to the wavefront passing therethrough, such as programmable deformable mirrors, pixelated liquid crystal arrays, or an "anti-sample", which is no more than such an adaptive optical element programmed to correct the phase of light passing through the element in order to compensate for the aberrations generated during the passage of the light through the sample. The nature of what such an adaptive optical element is, including "how it is made, how does it work, how does it adapt itself, and how does it changes itself to correct for refractive index variations in the sample, etc" as questioned by the Examiner, are thus known in the art and do not require further explanation.

The applicants therefore respectfully submit that claim 38, and its corresponding method claim 39 are thus enabled to one of skill in the art, and the applicants therefore request withdrawal of the Examiner's grounds of rejection of claims 38 and 39 under 35 U.S.C. 112, first paragraph.

Claim rejections - 35 USC § 102

Claims 34 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Berger et al. (article titled "Ray Tracing"; IEEE Computer Graphics & Applications). The Examiner states that:

"Berger discloses a computer implemented method comprising:

determining local variation of the refractive index at a multiplicity of locations in a medium ("refractive index squared is a linear function of the altitude within a layer of air at constant pressure" at page 37, right column); and

analytically determining the path of a ray through the multiplicity of locations in the medium, for a plurality of rays impinging thereon in different directions ("as the ray enters the mirage box, it strikes the different air layers, bending at each level and

thereby approximating the parabolic ray equation" at page 8, right column; see figures 3-5)."

The applicants respectfully submit that the assertion of the Examiner is incorrect. To the best of the applicants' understanding, Berger et al describes a parabolic ray path solution **only** for the case of mirages, where there is a gradient in the refractive index perpendicular to the ground. The Berger et al solution is therefore applicable only for the very specific geometry of parallel layers of refractive index, and for a specific functional dependence of the refraction on height.

In contrast to what is shown in Berger et al., amended claim 34 of the present application recites:

"Apparatus for ray tracing through a medium having multiple variations in refractive index including:

an image information acquirer providing information relating to local refractive index variations at **any** multiplicity of three dimensional locations in said medium, said local refractive index variations being determined by **any one of differential interference contrast (DIC) imaging, phase microscopy and fluorescence microscopy**; and

a computer employing an **analytically** determined path of a ray through the multiplicity of three dimensional locations in the medium, for a plurality of rays impinging thereon in different directions, by utilizing said local variation of the refractive index at said multiplicity of three dimensional locations in the medium." (Emphases added)

Nowhere in Berger et al is there mentioned or suggested :

(i) "providing information relating to local refractive index variations at **any** multiplicity of three dimensional locations in said medium"; or

(ii) "the determination of the refractive index variations by means of **differential interference contrast (DIC) imaging, phase microscopy and fluorescence microscopy**" since Berger et al use a simple layered model; or

(iii) "a computer employing an **analytically** determined path of a ray through the multiplicity of three dimensional locations in the medium";

all of which are now recited in amended claim 34.

The solution shown in Berger et al is a specific parabolic ray equation approximation, and this cannot be applied to the determination of the path of the light through any multiplicity of three dimensional locations in the medium, such as is possible using the methods of the present claimed invention, which is a most general analytical ray path and phase solution for curved rays when the refractive index is given at a multiplicity of three-dimensional locations in space, irrespective of the magnitude of change in the refractive index, and including the cases of reflections. Support for the elements of amended claim 34 are to be found in the specification on page 5, paragraph 2, and in the software appendix, from which it can be seen that the solution proposed is a general analytical solution for **any** geometrical arrangement of spatial refractive index variations.

The applicants therefore respectfully submit that the Berger et al prior art does not render claim 34 as being anticipated, and request withdrawal of the grounds of rejection of claim 34 under 35 USC 102(b). Similar arguments are applicable to corresponding method claim 35.

Claims 34 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Stam et al. (article titled "Ray Tracing in Non-Constant Media"; Proceeding of the 7th Eurographics Workshop on Rendering).

The Examiner has stated that :

"Stam discloses a computer implemented method comprising:

determining local variation of the refractive index at a multiplicity of locations in a medium ("a model of the refractive index" at section 4, first sentence); and

analytically determining the path of a ray through the multiplicity of locations in the medium, for a plurality of rays impinging thereon in different directions (section 5, "ray tracing algorithm, first paragraph; see "for each ray in the trace. . . ")."

The applicants respectfully submit that the assertion of the Examiner is incorrect. To the best of the applicants' understanding, Stam et al describes **a linear approximation** to ray tracing in continuously varying refractive index medium, using **a model** of the refractive index as a superposition of blobs. The approximate nature of the solution presented by Stam et al is stated clearly in the abstract, in section 4, and in section 5, first paragraph.

Furthermore, such a solution is applicable only for **small** perturbations in air. The description of a general air medium as a superposition of blobs is also applicable for small deviations in refractive index such as applied in air turbulence. The small perturbation nature of the Stam et al method is clear from the abstract, where it is stated:

[redacted]

In contrast to what is recited in amended claims 34 and 35 of the present application, nowhere in Stam et al is there mentioned or suggested **an analytical method** for determining the path of a ray through the multiplicity of three dimensional locations in the medium, as recited in amended claims 34 and 35. Furthermore, nowhere in Stam et al is there mentioned or suggested how the path of a ray through a multiplicity of three dimensional locations in the medium can be determined using the [redacted] local variations of the refractive index, as recited in amended claims 34 and 35.

Furthermore, in contrast to the limitation of the Stam et al method to small deviations of the refractive index, amended claims 34 and 35 have no limitation

whatsoever of the magnitude of the variation of the refractive indices which can be dealt with by the **analytically** determined path of a ray through the multiplicity of three dimensional locations in the medium.

The applicants therefore respectfully submit that the Stam et al prior art does not render claims amended 34 and 35 as being anticipated, and request withdrawal of the grounds of rejection under 35 USC 102(b).

Claim rejections - 35 USC § 103

Claim 40, which is representative of claim 41, is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Goldstein (US 4,827,125 A) and Chan et at. (US 6,275,726 Bl).

The Examiner has stated that:

“Goldstein discloses providing a confocal microscope (figure 1; "confocal... microscope" at column 4, line 37) having an imaging path between a three-dimensional sample (figure 1, numeral 27; "specimen" at column 8, line 6) and its output image plane (figure 1, numeral 35).

Goldstein does not teach:

determining variations of the refractive index in said three-dimensional sample; and

disposing in said imaging path a three-dimensional medium having properties that correct aberrations resulting from said variations of the refractive index in the three-dimensional sample.

Chan teaches imaging a specimen with a confocal microscope ("confocal" at column 2, line 30 and "confocal microscopy" at column 8, line 58), comprising:

determining variations of the refractive index in said three-dimensional sample ("highly light scattering because of the refractive index (n) variations among water and various inter/intra cellular components..." at column 1, lines 25-35); and

disposing in said imaging path a three-dimensional medium ("index matching

the cellular components" at column 2, line 37; "replacing inter and/or intrastitial (extracellular) fluid with another (replacement) fluid that has a refractive index more similar to that of the inter/intra cellular components" at column 2, lines 63-66) having properties that correct aberrations resulting from said variations of the refractive index in the three-dimensional sample ("enhancing the visualization of turbid biological tissue comprising the reduction of light reflection and refraction" at column 3, lines 29-31; "improves the imaging of tissues" and "improve the depth of penetration and increases signal to noise values" at column 8, lines 55-57).

It would have been obvious at the time the invention was made to one of ordinary skill in the art to dispose the index matching fluid of Chan into the specimen of Goldstein, in order to enhance "the visualization of turbid biological tissue comprising the reduction of light reflection and refraction" (Chan at column 3, lines 29-31), thereby improving "the imaging of tissues" and "the depth of penetration" and increasing "signal to noise values" (Chan at column 8, lines 55 - 57)."

The applicants respectfully submit that there is a fundamental difference between the invention described in Chan et al, and the claimed invention of the present application. In the Chan et al patent, to the best of the applicants' understanding, there are described "methods of reducing light attenuation in biological media or tissue that include index matching the cellular components of the biological media such that the amount of light reflection and refraction by the tissue is reduced." This is performed according to one embodiment, "by replacing inter and/or intrastitial (extracellular) fluid with another (replacement) fluid that has a refractive index more similar to that of the inter/intra cellular components".

However, to the best of the applicants' understanding, nowhere in Chan et al is there mentioned or suggested any **determination** of the refractive index of the sample. The Chan invention is concerned with matching of refractive indices of the cellular components of the sample with the inter and/or intrastitial (extracellular) fluid in order to improve visibility of the sample. The Chan et al invention relies on the values of refractive index of the various components known in advance, and is in no way

concerned with the **determination** of these refractive indices.

Additionally, to the best of the applicants' understanding, nowhere in Chan et al is there mentioned or suggested disposing a three-dimensional medium ..... **in the imaging path** between the sample and its output image plane. In the Chan et al patent, the three dimensional refractive index corrective medium is disposed within the sample itself, and not in the above described imaging path.

In contrast to the methods described in Chan et al, claim 40 of the present application recites:

"A method for confocal microscopy comprising the steps of:

providing a confocal microscope having an imaging path between a three-dimensional sample and its output image plane;

determining variations of the refractive index in said three-dimensional sample; and

disposing **in said imaging path** a three-dimensional medium with refractive properties that correct aberrations resulting from said variations of the refractive index in the three-dimensional sample." (Emphases added.)

The applicants therefore respectfully submit that no combination of Chan et al with any other prior art, whether the Goldstein patent cited by the Examiner, or any other reference, can render claims 40 and 41 of the present invention as obvious, and the applicants request withdrawal of the grounds of rejection of claims 40 and 41 under 35 USC 103(a).

Prior art

The Examiner has made of record prior art which is conpertinent to the applicants' disclosure and is not relied on.

U.S. 4,947,323 to Smith is pertinent to teaching deblurring of an image (Figure 1).

U.S. 6,166,853 to Sapia et al is pertinent as teaching 3D convolution of microscope images (abstract).

The applicants have carefully studied the above-referenced prior art documents, and to the best of their understanding thereof, none of this prior art affects the patentability of any of the applicants' claims, either alone or in combination with other prior art.

Conclusion

For all of the reasons set forth above, applicants respectfully submit that all of the pending claims 34, 35 and 38-41, as amended where applicable, are believed to be allowable. Reconsideration and prompt allowance of this application are therefore respectfully requested.

Respectfully submitted,

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